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(54) Oral pharmaceutical compositions for specific colon delivery.

(57) Oral pharmaceutical compositions consisting of:

a) a core containing the active principle or a mixture of active principles optionally combined with excipients;

b) an intermediate coating layer of said core, which can delay the release of the active principle contained in the core for the programmed time, independently of the pH;

c) an outer layer whose dissolution activates the process of swelling/dissolution/erosion of the intermediate coating layer of point b).

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The present invention refers to delayed release oral pharmaceutical compositions for specific colon delivery.

The selective release of drugs in the colon has recently become more and more important in view of a number of therapeutic applications such as the oral administration of proteins and peptides, the treatment of bacterial infections of colon, the administration of anti-tumor, anti-inflammatory or antimycotic agents.

The systems up-to-now used may be generally classified as relying either on a chemical approach or on a technological approach, the former consisting in the use of pro-drugs and the latter in the use of biodegradable polymers or polymers with pH-dependent solubility.

The different approach on which the present invention is based consists in the possibility of exploiting the remarkable regularity of the transit time of the small intestine (3±1 hours according to Davis S.S. et al., Gut, 27 (1986) 886): the system proposed relies on the use of a control mechanism which can recognize the entry into the small intestine and of a polymer or polymers or copolymers mixture preventing the drug release for the time needed to transit through the small intestine segment.

EP-A-0 366 621 discloses a similar colon selective delivery system including a core of a therapeutically active substance coated by three different layers: an inner layer including an anionic polymer, an outer gastroresistant layer and an intermediate swellable layer constituted by high viscosity cellulose.

This intermediate layer is constituted by cellulose derivatives with high molecular weight.

The aqueous solutions of these substances present a high viscosity, which strongly requires to use an organic solvent (in which the cellulose derivative is practically insoluble) for the application of the intermediate polymeric layer, in order to maintain acceptable the range of process cost and time.

We have surprisingly noticed that it is anyhow possible to obtain a considerable release delay using a low viscosity cellulose derivative film.

These derivatives show some advantages in respect of the ones of the mentioned patent, among which the most important is that their water solutions, at the concentrations suitable for film coating process, have a remarkable lower viscosity and therefore the use of filmogenic aqueous solutions is allowable; as certainly known, this represent a considerable advantage from the ecological and environmental point of view in respect to the use of organic solvents.

Furthermore the use of low viscosity polymers, characterized by a quicker solubilization or erosion time, allows to maintain at thinner levels the gel layer generated upon hydration, this allows to obtain a higher speed of release (improved burst effect, like a spike), when the desired delay time is reached.

The present invention refers to a core surrounded by only two layers of polymers, whereas the patent EP-A-0-366 621 is referred to a three layers system and, consequently, it needs a higher number of manufacturing steps, with the obvious rebounds on the production costs.

Moreover the cited patent describes a pH-dependent system, because the drug release is ultimately limited (after the delay due to the intermediate layer) by the inner layer, which must be dissolved to allow the drug to be released: this inner layer is in any case constituted by a polymer soluble only at a pH value equal or more than 7.

The present invention allows the following advantages to be reached:

1) a more flowable process because one layering step has been removed;

2) the achievement of a potential more rapid release after the programmed lag-phase (more bursting release slope);

3) a completely pH-independent release pattern after the system activation.

Moreover, a further advantage of this application should be considered the suitability of low viscosity polymers; in fact this allows to design an aqueous coating procedure instead of an organic solvent, where environmental and antipollution policy have to be respected. If the costs of waste treatment should be considered, an effective saving is so obviously achievable.

Of course, where necessary, an organic polymer dispersion can be advantageously used.

The system of the present invention, that is easier to manufacture and cheaper than the prior art systems, includes:

a) a core containing the active principle or a mixture of active principles, optionally combined with excipients;

b) an intermediate coating layer of said core, which can delay the release of the active principle, contained in the core, for the desired time, independently of the pH;

c) an outer layer (starter layer) whose dissolution activates the process of swelling/dissolution/erosion of the intermediate coating layer of point b), for instance the activation starts by "recognizing" the exit of the system from the stomach and the entry into the small intestine. The trigger point is represented by the change of pH after the pylorus.

The core containing the active principle may be differently formulated (tablets, capsules, soft capsules, mini-tablets, granules, pellets, spheronized crystals), so as to allow the prompt release of the active agent or a further controlled release, after the desired lag-phase. For this purpose, core excipient either conventional either able to form a matrix system may be used. Said core may also consist of the active principle alone, in crystalline or amorphous form.

In a typical embodiment, the intermediate coating layer consists in a hydrophylic gelling polymer or copolymer (swelling polymer) or mixture thereof starting its swelling when the system is activated (triggered) by the dissolution of the outer gastroresistant layer. The swelled layer surrounding the core must have suitable characteristics to grant the complete protection of the substances contained in the core from biological fluids for the time needed to reach the release site.

The used polymers usually include methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomers, polyvinyl alcohols, polyoxyethylene glycols, polyvinylpyrrolidones, poloxamers, natural or synthetic rubbers, polysaccharides or derivatives or mixtures thereof.

Besides the so called swellable polymers, other kinds of substances such as polysaccharides, polyaminoacids, polyalcohols, polyglycols or other ones having the capability of dissolving or becoming freely permeable with an exactly defined kinetic following hydration in aqueous fluids may be effectively used according to this invention. Examples of these substances are provided by gelatine, saccharose, sorbitol, mannanes, jaluronic acid or its synthetic derivatives or the like. The polymer may be applied on the core by different techniques, such as the spray coating or double tabletting (press-coating).

The hydrophilic intermediate polymeric layer is applied on the core until a weight gain, determined as solid substance, ranging between 10 and 300%, preferably between 50 and 150%, is reached.

In a preferred embodiment, the intermediate coating layer is composed, as unique or main component, by a cellulose derivative, preferably a hydroxypropylmethylcellulose giving a 2% aqueous solution with viscosity ranging from 5 to 100 mPa.s at room temperature.

The intermediate coating layer can further contain conventional auxiliary substances, such as hydrophobic materials like lubricants, flow promoting agents, plasticizers and antisticking agents. Examples of auxiliary substances are polyethylene glycol, polyvinylpyrrolidone, talc, magnesium stearate, glyceryl beenate, stearic acid, titanium dioxide.

The outer layer consists of a material whose dissolution is pH-dependent.

The gastroresistant outer layer may be obtained by using the polymers usually available to this purpose such as cellulose acetophthalate, cellulose acetate terephtalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, polyvinyl alcohol phthalate, polyacrylate or polymethacrylates.

The outer layer may optionally consist of hard or soft gelatine wall (capsules) coated by the above described gastroresistant polymers (i.e. the system consists of gastroresistant capsules filled with delayed release units).

Examples of active principles which may be used according to the invention comprise peptide or protein substances, ergot alkaloids or combinations thereof, hormone substances or their precursors, substances endowed with antimicrobial activity, like antiprotozoarian, antibacterial or antimycotic substances, immunomodulating, immunostimolant or immunosuppressive agents, vaccines, peptide hormone analogues or antagonists. Specific examples of these substances comprise posatirelin, protirelin, calcitonin, insulin, glutathione, hematopoietine, hirudin, cyclosporin, interferon, desmopressin, thymopentin, pidotimod.

It is comprised in the present invention a process for the preparation of the oral pharmaceutical compositions above described. Said process comprises the steps of

a) forming a core of active principle or of a mixture of active principles, optionally combined with excipients;

b) applying an intermediate coating layer on said core by means of a film coating or press-coating processes;

c) applying an outer layer on said intermediate coating layer.

In a preferred embodiment, the intermediate coating layer as to point b) is applied on said core until a weight gain, determined as solid substance, ranging from 10 to 300%, preferably from 50 to 150%, is reached.

The intermediate layer is applied on the core by means of a film coating process, either in a fluid bed apparatus or in a pan coat, or a atomization process, or a press coating process.

In a more preferred embodiment, the intermediate layer is applied on the core by means of a film coating process, by spraying an aqueous polymeric dispersion or an organic or hydro-organic solvent polymeric dispersion with a solid content ranging between 2 and 50% w/w, preferably ranging between 5 and 25 %.

The following non limitative examples further illustrate the invention.

In the examples, dissolution test was carried out according to the following standard method:
Acidic medium: 900 ml HCl 0.01 N
Neutral medium: 900 ml phosphate buffer pH 7.5
Temperature: 37 ° C
Apparatus: paddle (number 2 - according to USP XXII ed.) 50 RPM.

EXAMPLE 1

Tablets containing 20 mg of posatirelin are formulated by using an excipient mixture consisting of lactose, microcrystalline cellulose, polyvinylpyrrolidone and magnesium stearate. The tablets, obtained by direct compression, are fluid-bed coated with a Methocel E50-LV(TM) (showing a viscosity as high as 50 mPa.s at 2% aqueous solution) containing PEG as plasticizer. After intermediate layer deposition is completed, the tablets are made gastroresistant by applying a further coating layer of cellulose acetate phthalate containing diethylphthalate as plasticizer.

The dissolution test carried out on the finished systems showed the absence of release at pH lower than 5 for at least 2 hours. Upon increasing the pH of the dissolution medium up to 7.5 no drug release occours for the subsequent 4 hours; then 70% of the active agent is released within 45 minutes.

EXAMPLE 2

Tablet cores containing 4 mg of pidotimod are formulated using an excipient mixture consisting of dibasic calcium phosphate, microcrystalline cellulose, glyceryl beenate and silicon dioxide.

The tablets are then charged into a tabletting apparatus having three feeding stations, respectively filled with a mixture of carboxyvinylpolymer, polyvinylpyrrolidone and polyethylenglycol the first, with said cores the second one and with the cited polymer mixture of the first station the third one.

The obtained small diameter coated tablets are distributed into gelatine capsules which in turn are covered with a methacrylic ester suspension.

The drug release pattern of these systems, determined as above specified, shows the absence of drug release for the first 3 hours subsequent the change of pH medium (trigger point).

EXAMPLE 3

Crystalline dihydroergocristine mesylate is granulated in fluid bed and then coated in the same apparatus with a mixture of hydroxypropylmethylcellulose and ethylcellulose. The granules are partitioned in capsules of size 1, that are subsequently coated with a gastroresistant film.

The in-vitro release of the active principle is absent in acidic medium and in the neutral medium for the first 6 hours following the activation, then it slowly proceeds for 6 hours.

EXAMPLE 4

Tablet cores (180 mg weight, 6.7 mm diameter) containing 10 mg of posatireline are formulated using an excipient mixture consisting of dibasic calcium phosphate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The tablets, obtained by direct compression, show a complete drug dissolution within 5 minutes.

The tablets are coated in an automatic pan with an aqueous solution of Methocel E15-LV(TM). The solution contains PEG as plasticizer. Samples having different weight gains have been collected for examination at increasing times.

Subsequently the systems are coated again with an aqueous gastroresistant suspension of CAP, containing triacetine as plasticizer.

Dissolution tests performed on the collected samples have shown a good correlationship between weight gain relevant to intermediate coating layer and lag release time after activation:

WEIGHT GAINS after first coating	LAG-PHASE (MINUTES)
10%	10
20%	25
30%	35
40%	50
50%	70
70%	90
100%	130
125%	160
150%	200

EXAMPLE 5

Tablets of 180 mg weight containing 100 I.U. of salmon calcitonin, have been prepared; methylparaben has been used as release marker.

The tablets are press-coated in a tabletting unit with a low viscosity hydroxypropylmethylcellulose (Methocel E15-LV(T.M.); polyvinylpyrrolidone and magnesium stearate have been used as auxiliary substances. Subsequently the tablets are coated with an aqueous gastroresistant suspension of methacrylic ester suspension.

The release pattern has been demonstrated dependent on the HPMC type: in fact, taking constant the thickness of the coating all around (1.2 - 1.8 mm) a delay time of 100 minutes in achieving detectable levels of the marker has been obtained

EXAMPLE 6

Operating as described in the example 5, has been changed the polymer type of the intermediate layer: by using Methocel E50-LV(T.M.) a release delay of more than 160 minutes in the same conditions has been obtained.

EXAMPLE 7

Operating as described in the example 4, tablet cores containing 3.000.000 I.U. of natural extractive alfa-interferone and 5 mg of methylparaben as marker has been coated by spraying an hydroalcoholic (water - ethyl alcohol) dispersion of Methocel(TM) E50-LV at a 10% concentration containing also 5% of magnesium stearate, 2% of PVP and 1% of PEG 6000. A gastroresistant layer is then applied with the known method.

No drug release was observed during the first 2 hours in acidic medium and for at least 3 hours after the system activation.

Claims

1. Oral pharmaceutical compositions consisting of:
   a) a core containing the active principle or a mixture of active principles optionally combined with excipients;
   b) an intermediate coating layer of said core, which can delay the release of the active principle contained in the core for the programmed time, independently of the pH;
   c) an outer layer whose dissolution activates the process of swelling/dissolution/erosion of the intermediate coating layer of point b).

2. Compositions according to claim 1, wherein the intermediate coating layer described in point b) consists of a hydrophilic swellable polymer or copolymer or mixture thereof and the outer layer described in point c) consists of a material whose dissolution is promoted by the change of pH associated with the passage through the pylorous.

3. Compositions according to claim 2, wherein the hydrophilic polymer is selected from methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomers, polyvinyl

alcohols, polyoxyethylene glycols, polyvinylpyrrolidones, poloxamers, natural or synthetic rubbers, polysaccharides or derivatives or mixtures thereof.

4. Compositions according to claim 3, wherein the hydrophilic intermediate coating layer is applied on the core until a weight gain, determined as solid substance with respect to the core, ranging between 10 respect to the core, ranging between 10 and 300%, preferably between 50 and 150%.

5. Compositions according to claim 4, wherein the intermediate coating layer is composed, as unique or main component, by a cellulose derivative, preferably a hydroxypropylmethylcellulose giving a 2% aqueous solution with a viscosity ranging from 5 to 100 mPa.s at room temperature.

6. Compositions according to claim 5, wherein the intermediate coating layer contains conventional auxiliary substances, such as hydrophobic materials like lubricants, flow promoting agents, plasticizers and antisticking agents.

7. Compositions according to claim 6, wherein the auxiliary substances for the intermediate coating layer are selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, talc, magnesium stearate, glyceryl beenate, stearic acid, titanium dioxyde, triacetine, silicon dioxide.

8. Compositions according to any one of the preceding claims, wherein the outer layer consists of gastroresistant polymers or copolymers or mixtures thereof, preferably cellulose acetate phthalate or polymethacrylic derivatives.

9. Compositions according to any one of the preceding claims, wherein the outer layer consists of hard or soft gelatine wall (capsules) coated with gastroresistant polymers or copolymers.

10. Compositions according to any one of the preceding claims, wherein the active ingredient is posatirelin, protirelin, calcitonin, insulin, glutathione, hematopoietin, hirudin, cyclosporin, interferon, desmopressin, thymopentin, pidotimod.

11. A process for the preparation of oral pharmaceutical compositions of claims 1-10 comprising the steps of

a) forming a core of active principle or of a mixture of active principles, optionally combined with excipients;
b) applying an intermediate coating layer on said core by means of a film coating or press-coating processes;
c) applying an outer layer on said intermediate coating layer.

12. A process according to claim 11, wherein said intermediate coating layer as to point b) is applied on said core until a weight gain, determined as solid substance, ranging from 10 to 300%, preferably from 50 to 150%, is reached.

13. A process according to claims 11-12, wherein said intermediate layer is applied on the core by means of a film coating process, either in a fluid bed apparatus or in a pan coat, or a atomization process, or a press coating process.

14. A process according to claims 11-12, wherein the intermediate layer is applied on the core by means of a film coating process, by spraying an aqueous polymeric dispersion or an organic or hydro-organic solvent polymeric dispersion with a solid content ranging between 2 and 50% w/w, preferably ranging between 5 and 25%.